Immunosuppressive therapy mitigates immunological rejection of human embryonic stem cell xenografts.

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Public Summary:

Scientific Abstract:
Given their self-renewing and pluripotent capabilities, human embryonic stem cells (hESCs) are well poised as a cellular source for tissue regeneration therapy. However, the host immune response against transplanted hESCs is not well characterized. In fact, controversy remains as to whether hESCs have immune-privileged properties. To address this issue, we used in vivo bioluminescent imaging to track the fate of transplanted hESCs stably transduced with a double-fusion reporter gene consisting of firefly luciferase and enhanced GFP. We show that survival after transplant is significantly limited in immunocompetent as opposed to immunodeficient mice. Repeated transplantation of hESCs into immunocompetent hosts results in accelerated hESC death, suggesting an adaptive donor-specific immune response. Our data demonstrate that transplanted hESCs trigger robust cellular and humoral immune responses, resulting in intragraft infiltration of inflammatory cells and subsequent hESC rejection. Moreover, we have found CD4(+) T cells to be an important modulator of hESC immune-mediated rejection. Finally, we show that immunosuppressive drug regimens can mitigate the anti-hESC immune response and that a regimen of combined tacrolimus and sirolimus therapies significantly prolongs survival of hESCs for up to 28 days. Taken together, these data suggest that hESCs are immunogenic, trigger both cellular and humoral-mediated pathways, and, as a result, are rapidly rejected in xenogeneic hosts. This process can be mitigated by a combined immunosuppressive regimen as assessed by molecular imaging approaches.

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